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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/714,211	11/14/2003	Joseph Edward Zahner	NR 03-001	5750

7590 10/19/2006

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EXAMINER	
WOITACH, JOSEPH T	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 10/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/714,211	ZAHNER	
	Examiner	Art Unit	
	Joseph T. Woitach	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *pto-90*.

DETAILED ACTION

This application is a continuation of 09/919,298, filed July 31, 2001, now ABN, which claims benefit of 60/254,551, filed December 21, 2000.

Applicants' amendment filed July 24, 2006, has been received and entered. Claims 13-19 have been canceled. Claims 1-12 are pending.

Election/Restrictions

Applicant's election of Group I in the reply filed on July 27, 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-12 are pending. Claims drawn to non-eleceted inventions have been canceled. Claims 1-12, drawn to a method or reprogramming a keratinocyte comprising treating with an agent that promotes demethylation and an agent that inhibits deacetylation of a histone protein , are currently under examination.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the

application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." See list on pages 6-14, and single citations throughout. Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue

experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The claims are broadly drawn to reprogramming any species of keratinocyte cell into effectively any cell type by administering to said somatic cell an agent which promotes cellular reprogramming, and subsequently adding agents that differentiate the cell into a final product. Dependent claims recite specific agents which are known and used in the art to affect the methylation (5-aza-2'-deoxycytidine), acetylation (trichostatin A) and agents which affect the cell cycle (cyclin B). The specification provides a general outline for the basis of the invention, which is that during differentiation of a cell specific changes occur to the genome of the cell which destines the fate of a cell. The basis of the instant invention is to erase the changes which occur during differentiation, methylation patterns of the genome and acetylation of histones to restore the genome of a differentiated cell to a state which represents an undifferentiated stem cell. The specification provides a working example wherein an outer root sheath cell is removed,

treated with trichostatin A, then treats the cells with the differentiating agent retinoic acid to demonstrate that the trichostatin A treatment was effective in undifferentiating the outer root cell. The working example demonstrates that outer root cell treated with retinoic acid take on a morphology which appears to be neuron-like, however this is based on morphology and no specific neuronal markers are demonstrated. Except for the specific conditions set forth in the working examples, the specification provides no other specific conditions for the isolation or culturing conditions for other cell types.

As noted above, the agents specifically recited in the claims are known in the art and have been used extensively for studying specific effects of methylation and acetylation on gene regulation. The basis of the instant rejection focuses on the lack of specific guidance necessary to practice the instantly claimed method in its full breadth. In particular the breadth of the claim encompasses "re-programming" the keratinocyte into any cell type, totipotent, pluripotent, or any differentiated cell type. More generally, the instant invention is based on a concept which has been recognized in the art for determining the differentiation pathway of a cell, however the simplistic solution of applying an agent to a cell to reprogram a cell to become a totipotent stem cell with the specific agents contemplated is not supported by the art nor the evidence provided in the specification.

At the time of filing, Kikyo *et al.* (J Cell Sci, 2000) review the state of the art for nuclear reprogramming. Kikyo *et al.* review many of the of the known changes which occur in the development of a cell from fertilization to adult including changes in methylation, acetylation, and HMG- histone exchange (see summary in figure 1). As acknowledged in the instant specification, Kikyo et al. teach that the only method known in the art for returning a nucleus of

a somatic cell to a more pluripotent state is the use of nuclear transfer, the transfer of a somatic nucleus into an enucleated oocyte. Kikyo *et al.* teach that gene activation/deactivation during differentiation is a very complex process and probably determined by many factors. In summary of the art Kikyo *et al.* teach that affecting the somatic nucleus before nuclear transfer may provide a better nuclear donor, however such a simple approach is unlikely to resolve the complex issues concerning the cell biology of the somatic cell nuclei (page 16, second column). Similar conclusions are made by Walsh *et al.* who provide a review of the nature of differentiation as it is related to methylation of several genes known to alter expression in a tissue specific pattern (pages 26-27). Walsh et al. teach that the methylation-development hypothesis has been put forward however the data that supports this hypothesis is ambiguous (page 31, first column). Walsh et al. conclude based on previous results in the art and on their new evidence that methylation plays only a minor role in mammalian development, and that methylation is a consequence rather than a cause of transcriptional regulation.

The art teaches that with respect to acetylation, a similar complex story exists. Similar to Walsh *et al.*, Keohane *et al.* (Dev Biol, 1996) teach that acetylation is associated with X-inactivation in cells, however the role for acetylation is very complex, and conclude that global deactylation in X may be more important for stabilization and maintenance of the inactive state than initiation (page 628, second column) which would be contrary to the instantly claimed methods. In another example of the complexity for the consequence of actylation, Eickhoff *et al.* (Biol Chem, 2000) teach that trichostatin A treatment of cells alters gene expression, however it sensitizes and induces the cell to undergo apoptosis (page 1127), not dedifferentiation. Hou *et al.* (Exp Cell Res, 2002) teach that trichostatin A treatment of human cells in culture reduces

telomerase expression and activity in the cells. Telomerase activity is considered a hallmark gene for a undifferentiated cell and a requirement for sustained proliferation of a cell. In light of the teaching in the art that reprogramming a cell is a complex process and the evidence that the specific agents contemplated in the instantly claimed method clearly do not result in a pluripotent cell, it is found that the specification provides insufficient guidance to practice the method as instantly claimed. Without the necessary guidance in the specification and the lack of correlative working examples, the claims would require an undue amount of experimentation without a predictable degree of success on the part of the skilled artisan.

In view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Kominato et al., J. Biol. Chem., Vol. 274, 37240-37250, 1999.

Lenoir-Voiale *et al.* Dermatology Research 285:197-204 (1993) teaches the affect of retinoic acid on outer root sheath cells in culture.

You *et al.* BBRC 28:268-274 (2000) teaches the effect of retinoic acid on keratinocytes in culture.

Each of the above references provide a detailed analysis of cells treated by methods which are similar to those presented in the working examples in the instant specification.

Conclusion

No claim is allowed.

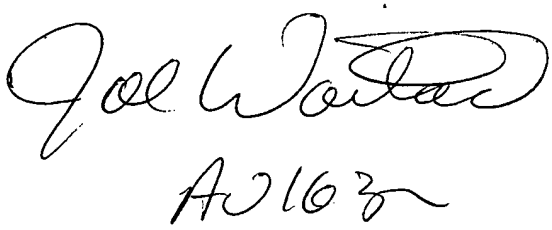
The claims are free of the art of record, because while the art does teach to treat some cells under the conditions instantly claimed, there is no specific teaching nor motivation to treat keratinocyte in such a way to provide for a re-programmed cell.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (571) 272-0739.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached at (571) 272-0735.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (571) 272-0532.

Joseph T. Woitach



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APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR / PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER
	20061016

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner for Patents

Drawings:

The color photographs and/or color drawings have been received and satisfy the requirements set forth in 37 CFR 1.84(b)(2). The petition filed under 37 CFR 1.84(a)(2) is granted.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (571) 272-0739.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached at (571) 272-0735.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (571) 272-0532.

Ram Shukla

RAM R. SHUKLA, PH.D.
SUPERVISORY PATENT EXAMINER